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MYERS BIGEL SIBLEY & SAJOVEC PO BOX 37428 RALEIGH, NC 27627			BADIO, BARBARA P	
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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 10/041,916

Filing Date: January 08, 2002

Appellant(s): LEONARD, THOMAS W.

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Devin R. Jensen  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed May 21, 2004.

**(1) *Real Party in Interest***

A statement identifying the real party in interest is contained in the brief.

**(2) *Related Appeals and Interferences***

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

**(3) *Status of Claims***

The statement of the status of the claims contained in the brief is correct.

**(4) *Status of Amendments After Final***

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) *Summary of Invention***

The summary of invention contained in the brief is correct.

**(6) *Issues***

The appellant's statement of the issues in the brief is correct.

**(7) *Grouping of Claims***

Appellant's brief includes a statement that claims 1-19 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

**(8) *ClaimsAppealed***

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(9) *Prior Art of Record***

4,154,820	SIMOONS	5-1979
5,288,717	RAVEENDRANATH et al.	2-1994
5,998,638	BENDER et al.	12-1999
5,998,639	RAIJMAKERS et al.	12-1999
6,458,778	KONG et al.	10-2002
6,525,039	SHAH et al.	2-2003

**(10) *Grounds of Rejection***

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raijmakers et al. ('639), Simoons ('820), Raveendranath et al. ('717), Shah et al. ('039), Bender et al. ('638) and Kong et al. ('778) in combination.

The claimed invention is a process for the production of a stable composition comprising a mixture of sulfated estrogens.

Raijmakers et al. teach sulfatation of estrogen mixtures (see the entire article, especially Examples 12-14).

Simoons teaches a stabilized composition of estrogens utilizing Tris (see Examples I-V, especially col. 7, lines 27-40).

Raveendranath et al. teach a process for the production of alkali metal 8,9-dehydroestrone sulfate esters and the production of a stabilized composition with Tris (see the entire article, especially col. 1, lines 36-63). The reference teaches mixture of 8,9-dehydroestrone with sodium hydride, reaction with trimethylamine-sulfur trioxide and addition of Tris (see Examples 1-7).

Each of Shah et al., Bender et al. and Kong et al. teach the production of sulfate esters of estrogens by reaction with a sulfur trioxide complex, such as trimethylamine-sulfur trioxide or triethylamine-sulfur trioxide (see the entire article, especially Example 1, '039; Example 1, '638; col. 13, lines 35-43, and col. 14, lines 65-67, '778). Shah also teaches the production of sulfate ester of an estrogen by first mixing said compound with sodium hydride before reacting with a sulfur trioxide (see Example 1, Method A).

The sulfatation of estrogen mixture would have been obvious to the skilled artisan at the time of the invention because (a) sulfatation of alcohols such as sterols utilizing a sulfur trioxide complex is well known in the art as evident by the Raveendranath, Shah, Bender and Kong; (b) addition of a stabilizer such as Tris to estrogenic compositions is also well known in the art as evident by Simoons and Raveendranath and (c) the level of skill of the ordinary artisan in the art at the time of the invention. The ordinary artisan in the art at the time of the invention would have the

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reasonable expectation that any alcohol or salt thereof, either alone or in combination with other alcohols or salts of said alcohols, would undergo sulfatation in the presence of any sulfatation agent, including a sulfur trioxide complex. Based on the teachings of the references as discussed above and the level of skill of the ordinary artisan in the art at the time of the invention, the claimed process is *prima facie* obvious. The motivation to make a stabilized composition comprising sulfated estrogens is based on the knowledge in the art that compositions comprising a mixture of estrogenic sulfate esters are useful in hormone replacement therapy (see for example, '820, col. 1, lines 20-31).

**(11) Response to Argument**

Appellant's argument is as followed:

(a) In regards to Claims 1-8, Appellant argues none of the references teach or suggest a process for producing a mixture of sulfated estrogens wherein the process involves reacting a mixture of at least two alkali metal salts of estrogens to provide a mixture of sulfated alkali metal salts of estrogens as recited by Claim 1;

(b) In regards to Claims 9-14, Appellant argues the references fail to teach or suggest the formation of a mixture of alkali metal salts of estrogens by reacting a mixture of estrogens with an alkali hydride in an apolar, aprotic solvent as recited by Claim 9; and

(c) In regards to Claims 15-19, Appellant argues the references fail to teach or suggest a process for a production of a stable composition comprising the reacting a mixture of at least two estrogens with sodium hydride as recited by claim 15. In essence,

Appellant's argument is that the cited references do not make obvious the utilization of a mixture of alkali metal salts or a mixture of estrogens in the prior art processes.

Appellant also argues "a prima facie obviousness rejection of Claims 1-19 is not supported by the combination of references because the references fail to teach or suggest all of the recitations of Claims 1-19 and the references fail to motivate a combination that teaches all or suggest all of the recitations". Appellant's argument was considered but not persuasive.

Compositions comprising at least two sulfated alkali metal salts of estrogens and Tris are well known in the art as evidenced by Raijmakers et al. and Simoons et al. The art also recognizes the use of said compositions for replacement therapy of estrogen deficiency associated with menopausal syndrome. Thus, the art provides the motivation to make claimed compositions comprising a mixture of sulfated alkali metal salt of estrogens. Appellant argues (a) Simoons et al. does not teach or suggest processes that may be used for the production of said alkali metal synthetic conjugated estrogen sulfate salts and (b) Raijmakers et al. does not propose a process wherein the formation of an alkali metal salt of estrogen occurs prior to sulfation nor does the reference suggest that the sulfation reactions could be performed in the same manner on alkali metal salts of estrogens.

Although, Simoons and Raijmakers do not teach the claimed process steps of (a) reacting a sulfur trioxide complex with alkali metal salts of estrogens and/or (b) reacting estrogens with sodium hydride in an apolar, aprotic solvent, said chemical reactions are known in the art. The process taught by Raveendranath et al., like the claimed

invention, relies on the initial production of an alkali metal salt of an estrogen by reaction of said compound with sodium hydride in an apolar, aprotic solvent followed by sulfation with a sulfur-trioxide complex and the addition of Tris as a stabilizer. The difference between the claimed invention and Raveendranath lies in the recitation of a starting material containing at least two estrogens or alkali metal salts thereof. In this regard, applicant argues Raveendranath does not propose the sulfation of other alkali metal salts of estrogens and the reference indicates the compounds formed are free from other conjugated esters. However, sulfation of other alkali metal salts of estrogens or corresponding alcohols thereof utilizing a sulfur-trioxide complex is known in the art as shown by Shah et al., Bender et al. and Kong et al. Shah teaches the production of the alkali metal salt of an estrogen by either (a) the initial production of an alkali metal salt followed by sulfation with a sulfur-trioxide complex as taught by Raveendranath or (b) sulfation of the corresponding alcohol with a sulfur-trioxide complex followed by production of an alkali metal salt of said sulfate as taught by Kong et al. and Bender et al.

In response to the teachings of Shah, Bender and Kong, Appellant argues (a) Shah involves the simultaneous reaction of an estrogen with sodium hydride, a sulfur-trioxide complex and a sodium hydroxide solution to produce the sulfate ester sodium salt and does not propose the reaction of a mixture of alkali metal salts with a sulfur-trioxide complex; (b) Bender does not propose the sulfation of an alkali metal salt of estrogen and (c) Kong does not propose reacting sulfur-trioxide complexes with an alkali metal salt of an estrogen.

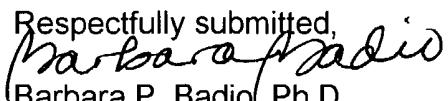
First, it is noted that Shah does not teach the simultaneous reaction of an estrogen with sodium hydride, a sulfur-trioxide complex and a sodium hydroxide solution as stated by applicant. Like the claimed invention, the reference teaches reaction of the estrogen with sodium hydride, followed by the addition of a sulfur-trioxide complex to said reaction mixture (see Examples 1-3 of the present specification). Shah also teaches a second method involving the production of an alkali metal salt utilizing sodium hydroxide (see Methods A and B of Example 1 of Shah).

Second, the issue is not whether each of the cited prior art teaches the claimed process but whether in combination they make obvious the claimed process. Because the prior art teaches each of the claimed reaction steps, the issue is whether it would have been obvious to utilize these steps using a starting material comprising a mixture of estrogens or alkali metal salts thereof with the reasonable expectation of obtaining a mixture of sulfated alkali metal salts of estrogens as recited by the instant claims. The cited prior art teach (a) utilization of different sterols in the production of alkali metal salt thereof by reaction of the said alcohols with sodium hydride and (b) sulfation of said alkali metal salt with a sulfur-trioxide complex (see Shah and Raveendranath). Based on said teachings, the skilled artisan in the art at the time of the invention would have the reasonable expectation that utilizing a starting material comprising a mixture of the sterols taught by the prior art in the prior art process would result in the production of a mixture of the desired sulfated alkali metal salts of the said compounds since each compound has been taught by the prior art to undergo sulfation using the prior art process.

Lastly, Appellant's statement that Raveendranath is distinguished from Rajmakers because the process of Rajmakers is "ineffective in the sulfation of 8,9-dehydroestrone" is noted. However, said is incorrect because Rajmakers exemplifies sulfation of 8,9-dehydroestrone (see Examples 12-14 of Rajmakers).

In summary, the prior art teaches (a) reaction of different alkali metal salts of estrogens with sulfur-trioxide complex and (b) production of said alkali metal salts by reacting the corresponding alcohol with sodium hydride. Based on said teachings, the skilled artisan would have the reasonable expectation that reaction of a mixture comprising two or more of said alkali metal salts of estrogens utilizing chemical reaction steps taught by the prior art would run to completion with the production of a mixture comprising said sulphated alkali metal salts of said estrogens. The motivation to make said composition is based on the teachings in the art that said compositions are useful in replacement therapy of estrogen deficiency associated with menopausal syndrome.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,  
  
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Primary Examiner  
Art Unit 1616

BB  
August 26, 2004

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